DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

PHILADELPHIA DISTRICT

900 U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19106

Telephone: 215-597-4390

WARNING LETTER

October 25, 2001

02-PHI-01

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Phillip B. Nelson, President
Enzyme Development Corporation
2 Penn Plaza, Suite 2439
New York, NY 10121-0034

Dear Mr. Nelson:

The agency has completed its review of the results of an inspection conducted at your active pharmaceutical ingredient (API) manufacturing facility located at 314 South Sherman Avenue in Scranton, Pennsylvania. The inspection was conducted from June 18 through July 3, 2001 by Philadelphia District Investigator Robert J. Maffei. At the conclusion of the inspection, Investigator Maffei issued form FDA 483, Inspectional Observations, to David C. Drazdauskas, Plant Manager, and discussed those observations with him. A copy of this form is enclosed for your information.

The inspection revealed significant deviations from good manufacturing practice as it relates to the production of Enzeco® Purified Papain II 56 (papain). These deviations cause this API to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) in that the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess. Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held in accordance with current good manufacturing practice. No distinction is made between active pharmaceutical ingredients or finished pharmaceuticals, and failure to conform with current good manufacturing practice constitutes a failure to comply with the requirements of the Act.

Specifically, the API is adulterated within the meaning of Section 501(a)(2)(B) as described below:

1. Your firm has not established the stability of papain.

The inspection revealed that your firm has not instituted a formal testing program or otherwise demonstrated the shelf life of the papain API you produce. We recommend that you include an

expiration date or retest date on the certificate of analysis issued with each lot of papain API. These dates should be supported by appropriate stability studies that ensure that the papain API will meet the quality attributes it is purported to meet when held in its marketed container/ closure system for its stated expiry or retest period.

2. Your firm has not demonstrated that cleaning procedures remove product residuals from non-dedicated equipment. In addition, your firm does not have written procedures for cleaning and does not document that cleaning was accomplished in accordance with written procedures.

The inspection revealed that your firm also manufactures enzyme products for the food and textile industries and that non-drug products are processed in the same blenders used to manufacture the papain API. These blenders are reportedly cleaned with hot potable water; the inspection revealed that, on at least two occasions, a non-drug product, [redacted] was blended with [redacted] which is insoluble in water, in each of the two blenders also used for the papain API. The next product produced in those blenders was the papain API. In addition, there was no documentation available to support that cleaning the blenders with hot potable water effectively removes residual product or that the blenders had, in fact, been cleaned and were acceptable for use to blend the papain API.

3. Your firm has not demonstrated that the analytical method used to determine enzyme activity of papain consistently produces reliable results.

The inspection revealed that your method, which provides for a measure of enzyme activity in values called tyrosine units (TU), uses a factor based on the current USP reference standard to convert the results from tyrosine units to USP units and that this factor is derived via a standard curve of tyrosine concentration. Your method requires that the standard curve be generated once every [redacted] The inspection revealed that your firm has generated this curve twice, once in January 1994 with USP reference standard lot F-3 and again in January 2001 with USP reference standard lot G. In addition, your firm has not demonstrated through appropriate, scientifically sound studies that your method will accurately determine enzyme activity and is suitable under its actual conditions of use.

4. Failure to ensure that each lot of API released conforms to its quality specifications.

The inspection revealed that your firm has identified specifications for pH and loss on drying which the papain API you produce are purported to meet. However, the inspection found that at least one lot of papain API manufactured in May 2001 was released without having been tested for pH and loss on drying. The agency expects that appropriate testing is performed on APIs prior to their release to ensure that the APIs conform to their established specifications.

5. Failure to demonstrate that the manufacturing process consistently produces APIs that meet their pre-determined quality specifications.

The inspection revealed that there is no documented evidence to support that your API blending operations, including reworking performed on lots returned to you by your customer, consistently produce a homogeneous API that conforms to its pre-determined specifications. The inspection also found that your firm forwards the papain API to a contract facility for [redacted] You should be aware that the agency considers this sterilization process to be an extension of the manufacturing process and that your firm should also demonstrate that the sterilization process performs as intended and does not adversely affect the quality of the finished papain API. In addition, batch production records for the papain API do not identify operating parameters such as blending times and speeds or the addition of extra raw materials done to adjust enzyme concentration and do not document that the performance of critical operating steps was checked by a person independent of the one performing the steps.

The inspection also revealed that your firm has not established written procedures for operations such as the use and calibration of laboratory equipment, the receipt and release of APIs and excipients, and sampling of the papain API. In addition, the inspection found that your firm does not keep records documenting that equipment is properly maintained.

Your firm must also take prompt action to register with the agency as a drug manufacturer and to file a drug listing form for the papain API. Failure to do so constitutes violations of Sections 510(b), 510(c), 510(d), and 510(j) of the Act. For information about how to register your manufacturing facility and list your drug product, please visit the agency's website at www.fda.gov/cder/drls/default.htm or call the Center for Drug Evaluation and Research's Information Management Team at 301-594-1086.

We have received your letters of July 19, 2001 and August 16, 2001, and we note that you have hired a consultant as well as a full time quality assurance manager. We have also received a letter dated September 26, 2001 from George Holmon, Quality Assurance Manager. While we note that Mr. Holmon's letter appears to address the observations listed on the form FDA 483, we find that, overall, his response does not provide sufficient detail to allow us to determine whether his corrective action plan will adequately address the deficiencies found during our inspection of your firm.

The above is not intended to be an all-inclusive list of deviations at your firm. As top management, it is your responsibility to assure that all of your company's operations are in compliance with the Act and its applicable regulations and requirements.

Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts. In

addition, pending new drug applications (NDA), abbreviated new drug applications (ANDA), or export approval requests may not be approved until the aforementioned deviations are corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include, but are not limited to, seizure and/or injunction.

Please advise this office in writing within fifteen (15) days of your receipt of this letter as to the specific actions you have taken or intend to take to correct these violations. Your reply should be directed to the attention of Karyn M. Campbell, Compliance Officer, at the address noted on the letterhead.

Sincerely,

Thomas D. Gardine

Thomas D. Gardine
District Director
Philadelphia District Office

Enclosure

cc: David C. Drazdauskas, Plant Manager
Enzyme Development Corporation
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Scranton, PA 18504

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Division of Primary Care and Home Health Services
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Harrisburg, PA 17104